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Filed on 30 June 1999 (30.06.1999)

(71) Applicant (for all designated States except US): THE GOVERNMENT OF THE UNITED STATES OF

AMERICA as represented by THE SECRETARY, DEPARTMENT OF HEALTH AND HUMAN SERVICES [US/US]; Office of Technology Transfer, National Institutes of Health, Suite 325, 6011 Executive Boulevard, Rockville, MD 20852 (US).

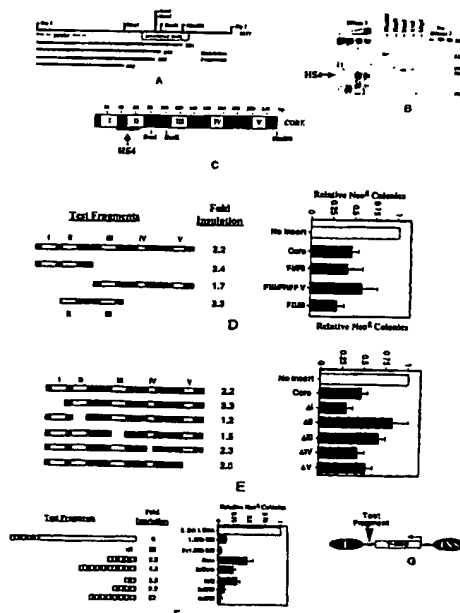
(72) Inventors; and
(75) Inventors/Applicants (for US only): BELL, Adam, C. [US/US]; 18670 Winding Creek Place, Germantown, MD 20874 (US). WEST, Adam, G. [US/US]; 4511 Everett Street, Kensington, MD 20985 (US). FELSENFELD, Gary [US/US]; 3109 Leland Street, Chevy Chase, MD 20815 (US).

(74) Agents: FEILER, William, S. et al.; Morgan & Finnegan, L.L.P., 345 Park Avenue, New York, NY 10154 (US).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT,

[Continued on next page]

(54) Title: DNA BINDING PROTEIN AND SEQUENCE AS INSULATORS HAVING SPECIFIC ENHANCER BLOCKING ACTIVITY FOR REGULATION OF GENE EXPRESSION



(57) Abstract: An insulator element shown to be both necessary and sufficient for the enhancer blocking activity in human cells is described. The insulator element of the invention is a 42 base pair DNA molecule having specific enhancer blocking activity for regulation of gene expression. The insulator element has also been shown to be the core binding site for CTCF, a DNA binding protein that is highly conserved in vertebrates. In addition, an insulator element containing CTCF binding sites has been identified in the region of the Igf 2 locus which is methylated exclusively on the paternal allele. Methylation of the insulator sequence abolishes the ability of CTCF to bind to the insulator and results in loss of enhancer-blocking activity.



LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL,
PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ,
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- (84) **Designated States (regional):** ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

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15/85, C07K 14/46, C12N 9/10, A61K 48/00

Street, Kensington, MD 20985 (US). **FELSENFELD, Gary** [US/US]; 3109 Leland Street, Chevy Chase, MD 20815 (US).

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(71) Applicant (*for all designated States except US*): **THE GOVERNMENT OF THE UNITED STATES OF AMERICA** as represented by **THE SECRETARY, DEPARTMENT OF HEALTH AND HUMAN SERVICES** [US/US]; Office of Technology Transfer, National Institutes of Health, Suite 325, 6011 Executive Boulevard, Rockville, MD 20852 (US).

Published:
— With international search report.

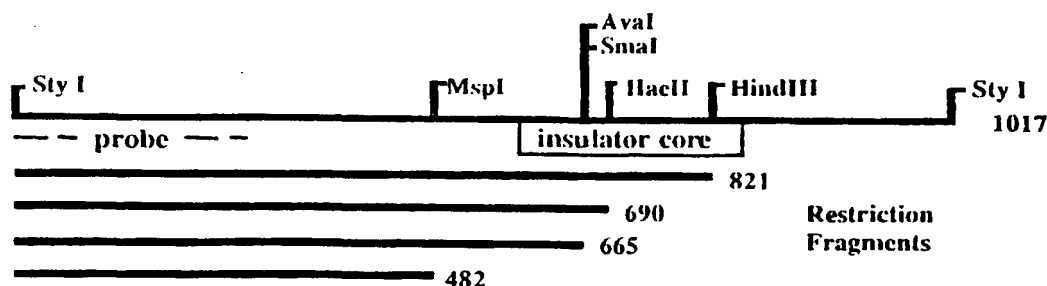
(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **BELL, Adam, C.** [US/US]; 18670 Winding Creek Place, Germantown, MD 20874 (US). **WEST, Adam, G.** [US/US]; 4511 Everett

(88) Date of publication of the international search report:
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(57) Abstract: An insulator element shown to be both necessary and sufficient for the enhancer blocking activity in human cells is described. The insulator element of the invention is a 42 base pair DNA molecule having specific enhancer blocking activity for regulation of gene expression. The insulator element has also been shown to be the core binding site for CTCF, a DNA binding protein that is highly conserved in vertebrates. In addition, an insulator element containing CTCF binding sites has been identified in the region of the Igf 2 locus which is methylated exclusively on the paternal allele. Methylation of the insulator sequence abolishes the ability of CTCF to bind to the insulator and results in loss of enhancer-blocking activity.

WO 01/02553 A3

PATENT COOPERATION TREATY

2026-4297 PC

K. Muller

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

Morgan & Finnegan, L.L.P.
Attn. Feiler, William S.
345 Park Avenue
New York, New York 10154

UNITED STATES OF AMERICA

ATTY

DUE

1 mo. call-up

BY

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION

(PCT Rule 44.1)

Date of mailing
(day/month/year)

05/01/2001

Applicant's or agent's file reference

2026-4297PC

FOR FURTHER ACTION

See paragraphs 1 and 4 below

International application No.

PCT/US 00/ 10509

International filing date
(day/month/year)

19/04/2000

Applicant

THE GOVERNMENT OF THE UNITED STATES OF AMERICA ...

1. ☒ The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

CASE 2026-4297 PC ATTY KAM

DUE March 5, 2001 (Art. 19.02)

1 mo. call-up February 5, 2001

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

U.S. SUPP. IDS

Name and mailing address of the International Searching Authority



European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Renate Jordan

CASE 2026-4297 PC ATTY KA

DUE April 5, 2001 (U.S. SUPP. IDS)

1 mo. call-up March 5, 2001

BY

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

2026-4297 PC

Muilex

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

Feiler, William S.
Morgan & Finnegan, L.L.P.
345 Park Avenue
New York, New York 10154
ETATS-UNIS D'AMERIQUE

PCT

WRITTEN OPINION

(PCT Rule 66)

Date of mailing
(day/month/year) 15.05.2001

Applicant's or agent's file reference
2026-4297PC

REPLY DUE within 3 month(s)
from the above date of mailing

International application No.

PCT/US00/10509

International filing date (day/month/year)

19/04/2000

Priority date (day/month/year)

30/06/1999

International Patent Classification (IPC) or both national classification and IPC

C12N15/00

Applicant

THE GOVERNMENT OF THE UNITED STATES OF AMERICA ...

1. This written opinion is the first drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

- I ☒ Basis of the opinion
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☒ Lack of unity of invention
- V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain document cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

3. The applicant is hereby invited to reply to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 30/10/2001.

CASE 2026-4297PC ATTY KAI

DUE August 15, 2001 (Written Opinion)

1 mo. call-up July 15, 2001

BY J-M

Name and mailing address of the international preliminary examining authority:



European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized officer / Examiner

Stoyanov, B

Formalities officer (incl. extension of time limits)

Emslander, S

Telephone No. +49 89 2399 8718



I. Basis of the opinion

1. With regard to the **elements** of the international application (Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed"):

Description, pages:

1-46 as originally filed

Claims, No.:

1-27 as originally filed

Drawings, sheets:

1-20 as originally filed

Sequence listing part of the description, pages:

1-24, filed with the letter of 26-05-2000

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☒ contained in the international application in written form.
- ☒ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

WRITTEN OPINION

International application No. PCT/US00/10509

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 22-24, 26, 27,

because:

- ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):
- ☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 22-24, 26, 27 are so unclear that no meaningful opinion could be formed (*specify*):
see separate sheet
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the said claims Nos. .

2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

- ☐ the written form has not been furnished or does not comply with the standard.
- ☐ the computer readable form has not been furnished or does not comply with the standard.

IV. Lack of unity of invention

1. In response to the invitation (Form PCT/IPEA/405) to restrict or pay additional fees, the applicant has:

- ☐ restricted the claims.

International application No. PCT/US00/10509

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with for the following reasons and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees:
see separate sheet

3. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this opinion:

☒ all parts.

☐ the parts relating to claims Nos. .

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

- ### 1. Statement

Novelty (N)	Claims	1-11, 13, 14, 16-21
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Inventive step (IS)	Claims 1-11, 13, 14, 16-21
---------------------	----------------------------

Industrial applicability (IA)	Claims
<p>1. A method for determining a value of a function $f(x)$ at a point x, comprising:</p> <p>receiving a set of data points (x_i, y_i) for $i = 1, 2, \dots, n$;</p> <p>fitting a function $f(x)$ to the data points;</p> <p>evaluating the function $f(x)$ at the point x.</p>	<p>1. A method for determining a value of a function $f(x)$ at a point x, comprising:</p> <p>receiving a set of data points (x_i, y_i) for $i = 1, 2, \dots, n$;</p> <p>fitting a function $f(x)$ to the data points;</p> <p>evaluating the function $f(x)$ at the point x.</p>

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

The examination is being carried out on the following application documents:

D1: CHUNG, J.H. ET AL.: 'Characterization of the chicken beta-globin insulator' PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, vol. 94, no. 2, 21 January 1997 (1997-01-21), pages 575-580, XP002155512 cited in the application

D2: FREVEL, M.A. ET AL.: 'A potential imprint control element: identification of a conserved 42 bp sequence upstream of H19' TRENDS IN GENETICS, vol. 15, no. 6, June 1999 (1999-06), pages 216-218, XP004170206 cited in the application

D3: WO 97 11972 A (THE TRUSTEES OF COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK) 3 April 1997 (1997-04-03)

Section III

According to the present wording of claims 22-24, 26 and 27 it is not clear in which manner the activation of the expression of a gene is actually achieved: such an activation may for instance occur due to the influence of the DNA binding domain of the fusion protein on the expression of the introduced gene, or also due to the influence of the methylase. It is also completely unclear if said components should be introduced into one and the same cell. Hence, this Authority is at present not in the position to establish an opinion with respect to inventive activity of these claims.

Section IV

The only common inventive concept underlying present international application can be seen in the provision of insulator elements for affecting the expression of a gene. However, taking into account that claimed insulator elements are known from D1 and D2 (see Section V below) said common inventive concept no longer exists. Correspondingly, present claims no longer relate to one invention, thus being in discordance to Rule 13.1-13.3 PCT. The opinion of this International Preliminary Examination Authority is that said international application relates to at least three separate inventions, namely:

Invention 1 (claims 1-15 completely, claim 27 partially)

An insulator element comprising SEQ ID Nos 1 and 100, having enhancer-blocking activity. A method of insulating/blocking the expression of a gene using said insulator element alone or in combination with the CTCF protein. A method for activating the expression of a gene using said insulator element in combination with CTCF.

Invention 2 (claims 16-21 completely, claim 27 partially)

Insulator elements comprising SEQ ID Nos 84-99 having CTCF dependent enhancer-blocking activity. A method of activating the expression of a gene using said insulators in combination with CTCF.

Invention 3 (claims 22-26 completely)

A method of activating the expression of a gene comprising inter alia the introduction of **any** insulator element in combination with a fusion protein, said fusion protein comprising a methylase and a DNA binding protein.

Section V

Document D1 discloses the properties of the chicken beta-globin insulator core element **comprising** SEQ ID No 1 of present international application (see e.g. Fig.3). D1 discloses also a number of expression constructs comprising said insulator core element (see for instance page 575 - materials and methods - and Fig. 2) operable in mammalian cells (see e.g. Fig. 1 and page 575 left column, first paragraph) and teaches that insulators can block activation of a promoter by an enhancer only when placed between them (see e.g. page 575, left column - first paragraph). D1 also teaches how to insulate the expression of a NEO-gene in K562 cells (see e.g. Fig. 1 and materials and methods), thus disclosing the subject matter of claims **1-11** of present international application. Concerning claims **3, 4, 6-9, 13** and **14** it is noted that the indication of use in a product claim is not considered suitable to limit the scope of such a claim; i.e. the claim is directed to the product per se (Guidelines CIII-4.8 PCT). To sum up: claims **1-11, 13** and **14** of **invention 1** are not in accordance with Article 33 (2)(3) PCT.

Document D2 discloses an imprint control element, conserved between mouse, rat and human, comprising SEQ ID NRs 84-98 (see e.g. FIG. 2), said element being located upstream of the H19 gene and possibly playing a role in the suppression of the neighbouring Igf2 gene (see e.g. page 216). Thus, claims 16-18 are not novel over D2. Furthermore, claims 19-21 are also not considered to be novel over D2, since the features defined in said claims may be an inherent property of said imprint control element. To sum up: claims 16-21 of **invention 2** are not in accordance with Article 33 (2)(3) PCT.

Section VII

With respect to the expression "incorporated by reference" (see e.g. page 10 line 25) applicants attention is drawn to the Guidelines II-4.17 PCT.

Section VIII

1) It is clear from the description on page 12 that the enhancer blocking activity of the chicken beta-globin insulator is dependent upon CTCF. Since claim 11 does not contain this essential feature it does not meet the requirement following from Article 6 PCT.

2) It is noted that the subject matter of claims 17 and 18 does not contain the technical feature "enhancer-blocking function".

3) Independent claim 22 does not contain all essential features, necessary to perform the subject matter of the claimed method, said essential features being disclosed in claims 23 and 25. Therefore claim 22 does not meet the requirement following from Article 6 PCT taken in combination with Rule 6.3(b) PCT.

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY
RECEIVED
DOCKET DEPT.

To:

Feiler, William S.
Morgan & Finnegan, L.L.P.
345 Park Avenue
New York, New York 10154
ETATS-UNIS D'AMERIQUE

2001 SEP 14 P 4: 31

PCT

MORGAN & FINNEGAN
NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT
(PCT Rule 71.1)Date of mailing
(day/month/year) 04.09.2001Applicant's or agent's file reference
2026-4297PC

IMPORTANT NOTIFICATION

International application No.
PCT/US00/10509International filing date (day/month/year)
19/04/2000Priority date (day/month/year)
30/06/1999

Applicant

THE GOVERNMENT OF THE UNITED STATES OF AMERICA ...

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized officer

Hingel, W

Tel. +49 89 2399-8717



PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 2026-4297PC	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US00/10509	International filing date (<i>day/month/year</i>) 19/04/2000	Priority date (<i>day/month/year</i>) 30/06/1999
International Patent Classification (IPC) or national classification and IPC C12N15/00		
Applicant THE GOVERNMENT OF THE UNITED STATES OF AMERICA ...		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☒ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 23/01/2001	Date of completion of this report 04.09.2001
Name and mailing address of the international preliminary examining authority: <div style="display: flex; align-items: center;"> <div> European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465 </div> </div>	Authorized officer Stoyanov, B Telephone No. +49 89 2399 7726



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US00/10509

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, pages:

1-46 as originally filed

Claims, No.:

1-27 as originally filed

Drawings, sheets:

1-20 as originally filed

Sequence listing part of the description, pages:

1-24, filed with the letter of 26-05-2000

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☒ contained in the international application in written form.
- ☒ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US00/10509

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 22-24, 26, 27.

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 22-24, 26, 27 are so unclear that no meaningful opinion could be formed (*specify*):
see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/10509

- ☐ restricted the claims.
- ☐ paid additional fees.
- ☐ paid additional fees under protest.
- ☐ neither restricted nor paid additional fees.
- 2. ☒ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.
- 3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is
 - ☐ complied with.
 - ☐ not complied with for the following reasons:
- 4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:
 - ☒ all parts.
 - ☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	12, 15, 25
	No:	Claims	1-11, 13, 14, 16-21
Inventive step (IS)	Yes:	Claims	12, 15, 25
	No:	Claims	1-11, 13, 14, 16-24, 26, 27
Industrial applicability (IA)	Yes:	Claims	1-27
	No:	Claims	

2. Citations and explanations see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US00/10509

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US00/10509

Reference is made to the following documents:

D1: CHUNG, J.H. ET AL.: 'Characterization of the chicken beta-globin insulator' PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, vol. 94, no. 2, 21 January 1997 (1997-01-21), pages 575-580, XP002155512 cited in the application

D2: FREVEL, M.A. ET AL.: 'A potential imprint control element: identification of a conserved 42 bp sequence upstream of H19' TRENDS IN GENETICS, vol. 15, no. 6, June 1999 (1999-06), pages 216-218, XP004170206 cited in the application

D3: WO 97 11972 A (THE TRUSTEES OF COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK) 3 April 1997 (1997-04-03)

Section III

According to the present wording of claims 22-24, 26 and 27 it is not clear in which manner the activation of the expression of a gene is actually achieved: such an activation may for instance occur due to the influence of the DNA binding domain of the fusion protein on the expression of the introduced gene, or also due to the influence of the methylase. It is also completely unclear if said components should be introduced into one and the same cell. Hence, this Authority is at present not in the position to establish an opinion with respect to inventive activity of these claims.

Section IV

The only common inventive concept underlying present international application can be seen in the provision of insulator elements for affecting the expression of a gene. However, taking into account that claimed insulator elements are known from D1 and D2 (see Section V below) said common inventive concept no longer exists. Correspondingly, present claims no longer relate to one invention, thus being in discordance to Rule 13.1-13.3 PCT. The opinion of this International Preliminary Examination Authority is that said international application relates to at least three separate inventions, namely:

Invention 1 (claims 1-15 completely, claim 27 partially)

An insulator element comprising SEQ ID Nos 1 and 100, having enhancer-blocking activity. A method of insulating/blocking the expression of a gene using said insulator element alone or in combination with the CTCF protein. A method for activating the expression of a gene using said insulator element in combination with CTCF.

Invention 2 (claims 16-21 completely, claim 27 partially)

Insulator elements comprising SEQ ID Nos 84-99 having CTCF dependent enhancer-blocking activity. A method of activating the expression of a gene using said insulators in combination with CTCF.

Invention 3 (claims 22-26 completely)

A method of activating the expression of a gene comprising inter alia the introduction of **any** insulator element in combination with a fusion protein, said fusion protein comprising a methylase and a DNA binding protein.

Section V

Document D1 discloses the properties of the chicken beta-globin insulator core element **comprising** SEQ ID No 1 of present international application (see e.g. Fig.3). D1 discloses also a number of expression constructs comprising said insulator core element (see for instance page 575 - materials and methods - and Fig. 2) operable in mammalian cells (see e.g. Fig. 1 and page 575 left column, first paragraph) and teaches that insulators can block activation of a promoter by an enhancer only when placed between them (see e.g. page 575, left column - first paragraph). D1 also teaches how to insulate the expression of a NEO-gene in K562 cells (see e.g. Fig.1 and materials and methods), thus disclosing the subject matter of claims **1-11** of present international application. Concerning claims **3, 4, 6-9, 13** and **14** it is noted that the indication of use in a product claim is not considered suitable to limit the scope of such a claim; i.e. the claim is directed to the product per se (Guidelines CIII-4.8 PCT). To sum up: claims **1-11, 13** and **14** of **invention 1** are not in accordance with Article 33 (2)(3) PCT.

Document D2 discloses an imprint control element, conserved between mouse, rat and human, comprising SEQ ID NRs 84-98 (see e.g. FIG. 2), said element being located upstream of the H19 gene and possibly playing a role in the suppression of the neighbouring Igf2 gene (see e.g. page 216). Thus, claims 16-18 are not novel over D2. Furthermore, claims 19-21 are also not considered to be novel over D2, since the features defined in said claims may be an inherent property of said imprint control element. To sum up: claims 16-21 of **invention 2** are not in accordance with Article 33 (2)(3) PCT.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US00/10509

Section VII

With respect to the expression "incorporated by reference" (see e.g. page 10 line 25) applicants attention is drawn to the Guidelines II-4.17 PCT.

Section VIII

- 1) It is clear from the description on page 12 that the enhancer blocking activity of the chicken beta-globin insulator is dependent upon CTCF. Since claim 11 does not contain this essential feature it does not meet the requirement following from Article 6 PCT.
- 2) It is noted that the subject matter of claims 17 and 18 does not contain the technical feature "enhancer-blocking function".
- 3) Independent claim 22 does not contain all essential features, necessary to perform the subject matter of the claimed method, said essential features being disclosed in claims 23 and 25. Therefore claim 22 does not meet the requirement following from Article 6 PCT taken in combination with Rule 6.3(b) PCT.

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner
 US Department of Commerce
 United States Patent and Trademark
 Office, PCT
 2011 South Clark Place Room
 CP2/5C24
 Arlington, VA 22202
 ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 06 March 2001 (06.03.01)	
International application No. PCT/US00/10509	Applicant's or agent's file reference 2026-4297PC
International filing date (day/month/year) 19 April 2000 (19.04.00)	Priority date (day/month/year) 30 June 1999 (30.06.99)
Applicant BELL, Adam, C. et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:
 23 January 2001 (23.01.01)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer C. Cupello Telephone No.: (41-22) 338.83.38
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PATENT COOPERATION TREATY

WO 01/02553
PCT/US00/10509

2026-4297 PC

From the INTERNATIONAL BUREAU

K. Muller

PCT

2001 JAN 23 P 12.57

NOTICE INFORMING THE APPLICANT OF THE
COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:

FEILER, William, S.
Morgan & Finnegan, L.L.P.
345 Park Avenue
New York, NY 10154
ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year)

11 January 2001 (11.01.01)

Applicant's or agent's file reference

2026-4297PC

IMPORTANT NOTICE

International application No.

PCT/US00/10509

International filing date (day/month/year)

19 April 2000 (19.04.00)

Priority date (day/month/year)

30 June 1999 (30.06.99)

Applicant

THE GOVERNMENT OF THE UNITED STATES OF AMERICA as represented by
THE SECRETARY, DEPARTMENT OF HEALTH et al

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
AG,AU,KP,KR,US

In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:

AE,AL,AM,AP,AT,AZ,BA,BB,BG,BR,BY,CA,CH,CN,CR,CU,CZ,DE,DK,DM,EA,EE,EP,ES,FI,GB,GD,
GE,GH,GM,HR,HU,ID,IL,IN,IS,JP,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MA,MD,MG,MK,MN,MW,MX,
NO,NZ,OA,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,TZ,UA,UG,UZ,VN,YU,ZA,ZW
The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
11 January 2001 (11.01.01) under No. WO 01/02553

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a demand for international preliminary examination must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the national phase, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

J. Zahra

Facsimile No. (41-22) 740.14.35

Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT/US00/10509

2026-42974
HC

PCT

From the INTERNATIONAL BUREAU

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

FEILER, William, S.
Morgan & Finnegan, L.L.P.
345 Park Avenue
New York, NY 10154
ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year) 30 June 2000 (30.06.00)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference 2026-4297PC	
International application No. PCT/US00/10509	
International publication date (day/month/year) Not yet published	
International filing date (day/month/year) 19 April 2000 (19.04.00)	Priority date (day/month/year) 30 June 1999 (30.06.99)
Applicant THE GOVERNMENT OF THE UNITED STATES OF AMERICA as represented by THE SECRETARY, DEPARTMENT OF HEALTH et al	

- The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
- This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.
- An asterisk(*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
- The letters "NR" appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

<u>Priority date</u>	<u>Priority application No.</u>	<u>Country or regional Office or PCT receiving Office</u>	<u>Date of receipt of priority document</u>
30 June 1999 (30.06.99)	60/141,728	US	21 June 2000 (21.06.00)

<p>The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland</p> <p>Facsimile No. (41-22) 740.14.35</p>	<p>Authorized officer Tessadel PAMPLIEGA <i>Tdp</i></p> <p>Telephone No. (41-22) 338.83.38</p>
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PATENT COOPERATION TREATY

2026-4297 PC

From the INTERNATIONAL BUREAU *L. Muller*

PCT

INFORMATION CONCERNING ELECTED
OFFICES NOTIFIED OF THEIR ELECTION

(PCT Rule 61.3)

To:

FEILER, William, S.
Morgan & Finnegan, L.L.P.
345 Park Avenue
New York, NY 10154
ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year) 06 March 2001 (06.03.01)		
Applicant's or agent's file reference 2026-4297PC		IMPORTANT INFORMATION
International application No. PCT/US00/10509	International filing date (day/month/year) 19 April 2000 (19.04.00) ✓	
		Priority date (day/month/year) 30 June 1999 (30.06.99) ✓
Applicant THE GOVERNMENT OF THE UNITED STATES OF AMERICA as represented by THE SECRETARY, DEPARTMENT OF HEALTH et al		

1. The applicant is hereby informed that the International Bureau has, according to Article 31(7), notified each of the following Offices of its election:

AP : GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW

EP : AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

National : AU, BG, CA, CN, CZ, DE, IL, JP, KP, KR, MN, NO, NZ, PL, RO, RU, SE, SK, US

2. The following Offices have waived the requirement for the notification of their election; the notification will be sent to them by the International Bureau only upon their request:

EA : AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

OA : BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

National : AE, AG, AL, AM, AT, AZ, BA, BB, BR, BY, CH, CR, CU, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IN, IS, KE, KG, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MW, MX, PT, SD, SG, SI, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW

3. The applicant is reminded that he must enter the "national phase" before the expiration of 30 months from the priority date before each of the Offices listed above. This must be done by paying the national fee(s) and furnishing, if prescribed, a translation of the international application (Article 39(1)(a)), as well as, where applicable, by furnishing a translation of any annexes of the international preliminary examination report (Article 36(3)(b) and Rule 74.1).

Some offices have fixed time limits expiring later than the above-mentioned time limit. For detailed information about the applicable time limits and the acts to be performed upon entry into the national phase before a particular Office, see Volume II of the PCT Applicant's Guide.

The entry into the European regional phase is postponed until 31 months from the priority date for all States designated for the purposes of obtaining a European patent.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer: C. Cupello <i>Cupello</i>
Facsimile No. (41-22) 740.14.35	Telephone No. (41-22) 338.83.38

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference
(if desired) (12 characters maximum) 2026-4297PC

Box No. I TITLE OF INVENTION
DNA BINDING PROTEIN AND SEQUENCE AS INSULATORS HAVING SPECIFIC
ENHANCER BLOCKING ACTIVITY FOR REGULATION OF GENE EXPRESSION

Box No. II APPLICANT

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

The Government of the United States of America
as represented by the Secretary, Department of
Health and Human Services
Office of Technology Transfer
National Institutes of Health
6011 Executive Boulevard, Suite 325
Rockville, Maryland 20852
US

☐ This person is also inventor.

Telephone No.
(301) 496-7056

Facsimile No.
(301) 402-0220

Teleprinter No.

State (that is, country) of nationality: US

State (that is, country) of residence: US

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

BELL, Adam C.
18670 Winding Creek Place
Germantown, Maryland 20874
US

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality: US

State (that is, country) of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

FEILER, William S. and CHEN, Haiyan
Morgan & Finnegan, L.L.P.
345 Park Avenue
New York, New York 10154
US

Telephone No.
(212) 758-4800

Facsimile No.
(212) 751-6849

Teleprinter No.

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

WEST, Adam G.
4511 Everett Street
Kensington, Maryland 20985
US

This person is:

☐ applicant only☒ applicant and inventor☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:

US

State (that is, country) of residence:

US

This person is applicant for the purposes of:

☐ all designated States☐ all designated States except the United States of America☒ the United States of America only☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

FELSENFELD, Gary
3109 Leland Street
Chevy Chase, Maryland 20815
US

This person is:

☐ applicant only☒ applicant and inventor☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:

US

State (that is, country) of residence:

US

This person is applicant for the purposes of:

☐ all designated States☐ all designated States except the United States of America☒ the United States of America only☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

☐ applicant only☐ applicant and inventor☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant for the purposes of:

☐ all designated States☐ all designated States except the United States of America☐ the United States of America only☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

☐ applicant only☐ applicant and inventor☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant for the purposes of:

☐ all designated States☐ all designated States except the United States of America☐ the United States of America only☐ the States indicated in the Supplemental Box☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) (mark the applicable check-boxes; at least one must be marked):

Regional Patent

- ☒ **AP ARIPO Patent:** GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☒ **EA Eurasian Patent:** AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ **EP European Patent:** AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ **OA OAPI Patent:** BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (if other kind of protection or treatment desired, specify on dotted line)

National Patent (if other kind of protection or treatment desired, specify on dotted line):

- | | |
|---|--|
| <input checked="" type="checkbox"/> AE United Arab Emirates | <input checked="" type="checkbox"/> LR Liberia |
| <input checked="" type="checkbox"/> AL Albania | <input checked="" type="checkbox"/> LS Lesotho |
| <input checked="" type="checkbox"/> AM Armenia | <input checked="" type="checkbox"/> LT Lithuania |
| <input checked="" type="checkbox"/> AT Austria | <input checked="" type="checkbox"/> LU Luxembourg |
| <input checked="" type="checkbox"/> AU Australia | <input checked="" type="checkbox"/> LV Latvia |
| <input checked="" type="checkbox"/> AZ Azerbaijan | <input checked="" type="checkbox"/> MA Morocco |
| <input checked="" type="checkbox"/> BA Bosnia and Herzegovina | <input checked="" type="checkbox"/> MD Republic of Moldova |
| <input checked="" type="checkbox"/> BB Barbados | <input checked="" type="checkbox"/> MG Madagascar |
| <input checked="" type="checkbox"/> BG Bulgaria | <input checked="" type="checkbox"/> MK The former Yugoslav Republic of Macedonia |
| <input checked="" type="checkbox"/> BR Brazil | <input checked="" type="checkbox"/> MN Mongolia |
| <input checked="" type="checkbox"/> BY Belarus | <input checked="" type="checkbox"/> MW Malawi |
| <input checked="" type="checkbox"/> CA Canada | <input checked="" type="checkbox"/> MX Mexico |
| <input checked="" type="checkbox"/> CH and LI Switzerland and Liechtenstein | <input checked="" type="checkbox"/> NO Norway |
| <input checked="" type="checkbox"/> CN China | <input checked="" type="checkbox"/> NZ New Zealand |
| <input checked="" type="checkbox"/> CR Costa Rica | <input checked="" type="checkbox"/> PL Poland |
| <input checked="" type="checkbox"/> CU Cuba | <input checked="" type="checkbox"/> PT Portugal |
| <input checked="" type="checkbox"/> CZ Czech Republic | <input checked="" type="checkbox"/> RO Romania |
| <input checked="" type="checkbox"/> DE Germany | <input checked="" type="checkbox"/> RU Russian Federation |
| <input checked="" type="checkbox"/> DK Denmark | <input checked="" type="checkbox"/> SD Sudan |
| <input checked="" type="checkbox"/> DM Dominica | <input checked="" type="checkbox"/> SE Sweden |
| <input checked="" type="checkbox"/> EE Estonia | <input checked="" type="checkbox"/> SG Singapore |
| <input checked="" type="checkbox"/> ES Spain | <input checked="" type="checkbox"/> SI Slovenia |
| <input checked="" type="checkbox"/> FI Finland | <input checked="" type="checkbox"/> SK Slovakia |
| <input checked="" type="checkbox"/> GB United Kingdom | <input checked="" type="checkbox"/> SL Sierra Leone |
| <input checked="" type="checkbox"/> GD Grenada | <input checked="" type="checkbox"/> TJ Tajikistan |
| <input checked="" type="checkbox"/> GE Georgia | <input checked="" type="checkbox"/> TM Turkmenistan |
| <input checked="" type="checkbox"/> GH Ghana | <input checked="" type="checkbox"/> TR Turkey |
| <input checked="" type="checkbox"/> GM Gambia | <input checked="" type="checkbox"/> TT Trinidad and Tobago |
| <input checked="" type="checkbox"/> HR Croatia | <input checked="" type="checkbox"/> TZ United Republic of Tanzania |
| <input checked="" type="checkbox"/> HU Hungary | <input checked="" type="checkbox"/> UA Ukraine |
| <input checked="" type="checkbox"/> ID Indonesia | <input checked="" type="checkbox"/> UG Uganda |
| <input checked="" type="checkbox"/> IL Israel | <input checked="" type="checkbox"/> US United States of America |
| <input checked="" type="checkbox"/> IN India |continuation-in-part..... |
| <input checked="" type="checkbox"/> IS Iceland | <input checked="" type="checkbox"/> UZ Uzbekistan |
| <input checked="" type="checkbox"/> JP Japan | <input checked="" type="checkbox"/> VN Viet Nam |
| <input checked="" type="checkbox"/> KE Kenya | <input checked="" type="checkbox"/> YU Yugoslavia |
| <input checked="" type="checkbox"/> KG Kyrgyzstan | <input checked="" type="checkbox"/> ZA South Africa |
| <input checked="" type="checkbox"/> KP Democratic People's Republic of Korea | <input checked="" type="checkbox"/> ZW Zimbabwe |
| <input checked="" type="checkbox"/> KR Republic of Korea | Check-boxes reserved for designating States which have become party to the PCT after issuance of this sheet: |
| <input checked="" type="checkbox"/> KZ Kazakhstan | <input checked="" type="checkbox"/> AG Antigua and Barbuda |
| <input checked="" type="checkbox"/> LC Saint Lucia | <input type="checkbox"/> |
| <input checked="" type="checkbox"/> LK Sri Lanka | |

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)

Box No. VI PRIORITY CLAIM☐ Further priority claims are indicated in the Supplemental Box.

Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is:		
		national application: country	regional application:* regional Office	international application: receiving Office
item (1) 30 June 1999 (30.06.99)	60/141,728	US		
item (2)				
item (3)				

☒ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office) identified above as item(s): (1)

* Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA)
(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):

ISA / EP

Request to use results of earlier search; reference to that search (if an earlier search has been carried out by or requested from the International Searching Authority):

Date (day/month/year)

Number

Country (or regional Office)

Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following number of sheets:

request : 5

description (excluding sequence listing part) : 46

claims : 4

abstract : 1

drawings : 15

sequence listing part of description : 24

Total number of sheets : 95

This international application is accompanied by the item(s) marked below:


1. ☒ fee calculation sheet (in duplicate)
2. ☒ separate signed power of attorney (unsigned)
3. ☒ copy of general power of attorney; reference number, if any:
4. ☐ statement explaining lack of signature
5. ☐ priority document(s) identified in Box No. VI as item(s):
6. ☐ translation of international application into (language):
7. ☐ separate indications concerning deposited microorganism or other biological material
8. ☒ nucleotide and/or amino acid sequence listing in computer readable form
Statement under 37 CFR §1.821(f) and WIPO Standard ST.25; Transmittal Letter
9. ☒ other (specify):

Figure of the drawings which should accompany the abstract: Fig. 1

Language of filing of the international application: English

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).


William S. Feiler
Agent for Applicants

For receiving Office use only		2. Drawings: <input type="checkbox"/> received: <input type="checkbox"/> not received:
1. Date of actual receipt of the purported international application:		
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:		
4. Date of timely receipt of the required corrections under PCT Article 11(2):		
5. International Searching Authority (if two or more are competent): ISA /	6. <input type="checkbox"/> Transmittal of search copy delayed until search fee is paid.	

For International Bureau use only
Date of receipt of the record copy by the International Bureau:

Supplemental Box *If the Supplemental Box is not used, this sheet should not be included in the request.*

1. *If, in any of the Boxes, the space is insufficient to furnish all the information: in such case, write "Continuation of Box No. ..." [indicate the number of the Box] and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient, in particular:*
 - (i) *if more than two persons are involved as applicants and/or inventors and no "continuation sheet" is available: in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below;*
 - (ii) *if, in Box No. II or in any of the sub-boxes of Box No. III, the indication "the States Indicated in the Supplemental Box" is checked: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant;*
 - (iii) *if, in Box No. II or in any of the sub-boxes of Box No. III, the inventor or the inventor/applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor;*
 - (iv) *if, in addition to the agent(s) indicated in Box No. IV, there are further agents: in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV;*
 - (v) *if, in Box No. V, the name of any State (or OAPI) is accompanied by the indication "patent of addition," or "certificate of addition," or if, in Box No. V, the name of the United States of America is accompanied by an indication "continuation" or "continuation-in-part": in such case, write "Continuation of Box No. V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI), the number of the parent title or parent application and the date of grant of the parent title or filing of the parent application;*
 - (vi) *if, in Box No. VI, there are more than three earlier applications whose priority is claimed: in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI;*
 - (vii) *if, in Box No. VI, the earlier application is an ARIPO application: in such case, write "Continuation of Box No. VI", specify the number of the item corresponding to that earlier application and indicate at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed.*
2. *If, with regard to the precautionary designation statement contained in Box No. V, the applicant wishes to exclude any State(s) from the scope of that statement: in such case, write "Designation(s) excluded from precautionary designation statement" and indicate the name or two-letter code of each State so excluded.*
3. *If the applicant claims, in respect of any designated Office, the benefits of provisions of the national law concerning non-prejudicial disclosures or exceptions to lack of novelty: in such case, write "Statement concerning non-prejudicial disclosures or exceptions to lack of novelty" and furnish that statement below.*

Continuation of Box No. V - Designation of States

US United States of America - continuation-in-part of US Provisional
Application Serial No. 60/141,728
filed 30 June 1999 (30.06.99)

PCT

FEE CALCULATION SHEET

Annex to the Request

For receiving Office use only

International application No.

Applicant's or agent's
file reference

2026-4297PC

Date stamp of the receiving Office

Applicant

The Government of the United States of America as represented by the Secretary, Department of Health and Human Services, et al.

CALCULATION OF PRESCRIBED FEES

1. TRANSMITTAL FEE \$ 240.00 ☐ T

2. SEARCH FEE \$ 990.00 ☐ S

International search to be carried out by EP
(If two or more International Searching Authorities are competent in relation to the international application, indicate the name of the Authority which is chosen to carry out the international search.)

3. INTERNATIONAL FEE

Basic Fee

The international application contains 95 sheets.

first 30 sheets \$ 427.00 ☐ b1

65 x \$10.00 = & 650.00 ☐ b2
remaining sheets additional amount

Add amounts entered at b1 and b2 and enter total at B \$ 1,077.00 ☐ B

Designation Fees

The international application contains 84 designations.

8 x \$92.00 = \$ 736.00 ☐ D

number of designation fees payable (maximum 8) amount of designation fee

Add amounts entered at B and D and enter total at I \$1,813.00 ☐ I

(Applicants from certain States are entitled to a reduction of 75% of the international fee. Where the applicant is (or all applicants are) so entitled, the total to be entered at I is 25% of the sum of the amounts entered at B and D.)

4. FEE FOR PRIORITY DOCUMENT (if applicable) \$ 15.00 ☐ P

5. TOTAL FEES PAYABLE \$3,058.00

Add amounts entered at T, S, I and P, and enter total in the TOTAL box

TOTAL

☐ The designation fees are not paid at this time.

MODE OF PAYMENT

☐ authorization to charge
deposit account (see below)

☒ cheque

☐ postal money order

☐ bank draft

☐ cash

☐ revenue stamps

☐ coupons

☐ other (specify):

DEPOSIT ACCOUNT AUTHORIZATION (this mode of payment may not be available at all receiving Offices)

The RO/ US ☐ is hereby authorized to charge the total fees indicated above to my deposit account.

☒ (this check-box may be marked only if the conditions for deposit accounts of the receiving Office so permit) is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account.

☒ is hereby authorized to charge the fee for preparation and transmittal of the priority document to the International Bureau of WIPO to my deposit account.

13-4500

Deposit Account No.

19 April 2000

Date (day/month/year)

Signature William S. Feiler

P. INT COOPERATION TREA

2026-4297
HK

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF RECEIPT OF
RECORD COPY

(PCT Rule 24.2(a))

To:

FEILER, William, S.
Morgan & Finnegan, L.L.P.
345 Park Avenue
New York, NY 10154
ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year) 21 June 2000 (21.06.00)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference 2026-4297PC	International application No. PCT/US00/10509

The applicant is hereby notified that the International Bureau has received the record copy of the international application as detailed below.

Name(s) of the applicant(s) and State(s) for which they are applicants:

THE GOVERNMENT OF THE UNITED STATES OF AMERICA as represented by THE SECRETARY,
DEPARTMENT OF HEALTH AND HUMAN SERVICES (for all designated States except US)
BELL, Adam, C. et al (for US)

International filing date : 19 April 2000 (19.04.00)
Priority date(s) claimed : 30 June 1999 (30.06.99)
Date of receipt of the record copy
by the International Bureau : 30 May 2000 (30.05.00)
List of designated Offices :

AP : GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW

EA : AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

EP : AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

OA : BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

National : AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI,
GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG,
MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU,
ZA, ZW

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer:

V. Gross

Telephone No. (41-22) 338.83.38

NOTIFICATION OF RECEIPT OF RECORD COPY

Date of mailing (day/month/year) 21 June 2000 (21.06.00)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference 2026-4297PC	International application No. PCT/US00/10509

ATTENTION

The applicant should carefully check the data appearing in this Notification. In case of any discrepancy between these data and the indications in the international application, the applicant should immediately inform the International Bureau.

In addition, the applicant's attention is drawn to the information contained in the Annex, relating to:

- ☒ time limits for entry into the national phase
- ☒ confirmation of precautionary designations
- ☒ requirements regarding priority documents

A copy of this Notification is being sent to the receiving Office and to the International Searching Authority.

INFORMATION ON TIME LIMITS FOR ENTERING THE NATIONAL PHASE

The applicant is reminded that the "national phase" must be entered before each of the designated Offices indicated in the Notification of Receipt of Record Copy (Form PCT/IB/301) by paying national fees and furnishing translations, as prescribed by the applicable national laws.

The time limit for performing these procedural acts is **20 MONTHS** from the priority date or, for those designated States which the applicant elects in a demand for international preliminary examination or in a later election, **30 MONTHS** from the priority date, provided that the election is made before the expiration of 19 months from the priority date. Some designated (or elected) Offices have fixed time limits which expire even later than 20 or 30 months from the priority date. In other Offices an extension of time or grace period, in some cases upon payment of an additional fee, is available.

In addition to these procedural acts, the applicant may also have to comply with other special requirements applicable in certain Offices. **It is the applicant's responsibility** to ensure that the necessary steps to enter the national phase are taken in a timely fashion. Most designated Offices do not issue reminders to applicants in connection with the entry into the national phase.

For detailed information about the procedural acts to be performed to enter the national phase before each designated Office, the applicable time limits and possible extensions of time or grace periods, and any other requirements, see the relevant Chapters of Volume II of the PCT Applicant's Guide. Information about the requirements for filing a demand for international preliminary examination is set out in Chapter IX of Volume I of the PCT Applicant's Guide.

GR and ES became bound by PCT Chapter II on 7 September 1996 and 6 September 1997, respectively, and may, therefore, be elected in a demand or a later election filed on or after 7 September 1996 and 6 September 1997, respectively, regardless of the filing date of the international application. (See second paragraph above.)

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

CONFIRMATION OF PRECAUTIONARY DESIGNATIONS

This notification lists only specific designations made under Rule 4.9(a) in the request. It is important to check that these designations are correct. Errors in designations can be corrected where precautionary designations have been made under Rule 4.9(b). The applicant is hereby reminded that any precautionary designations may be confirmed according to Rule 4.9(c) before the expiration of 15 months from the priority date. If it is not confirmed, it will automatically be regarded as withdrawn by the applicant. There will be no reminder and no invitation. Confirmation of a designation consists of the filing of a notice specifying the designated State concerned (with an indication of the kind of protection or treatment desired) and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.

REQUIREMENTS REGARDING PRIORITY DOCUMENTS

For applicants who have not yet complied with the requirements regarding priority documents, the following is recalled.

Where the priority of an earlier national, regional or international application is claimed, the applicant must submit a copy of the said earlier application, certified by the authority with which it was filed ("the priority document") to the receiving Office (which will transmit it to the International Bureau) or directly to the International Bureau, before the expiration of 16 months from the priority date, provided that any such priority document may still be submitted to the International Bureau before that date of international publication of the international application, in which case that document will be considered to have been received by the International Bureau on the last day of the 16-month time limit (Rule 17.1(a)).

Where the priority document is issued by the receiving Office, the applicant may, instead of submitting the priority document, request the receiving Office to prepare and transmit the priority document to the International Bureau. Such request must be made before the expiration of the 16-month time limit and may be subjected by the receiving Office to the payment of a fee (Rule 17.1(b)).

If the priority document concerned is not submitted to the International Bureau or if the request to the receiving Office to prepare and transmit the priority document has not been made (and the corresponding fee, if any, paid) within the applicable time limit indicated under the preceding paragraphs, any designated State may disregard the priority claim, provided that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity to furnish the priority document within a time limit which is reasonable under the circumstances.

Where several priorities are claimed, the priority date to be considered for the purposes of computing the 16-month time limit is the filing date of the earliest application whose priority is claimed.